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EXAMINER

PROUTY, REBECCA E

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1652

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10/07/2010

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Claims 1-17 are still at issue and are present for examination.

Applicants' arguments filed on 7/1/10, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 6-17 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/05/09.

Claims 1-5 are objected to as reciting non-elected subject matter.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (upon which claims 2-5 depend) as amended is confusing in the recitation of "is in sequence alignment with SEQ ID NO:1" as any two amino acid sequence can be aligned with one another. The sequences may have more or less identity to each other but it is unclear how any amino acid sequence could

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not be in sequence alignment with SEQ ID NO:1. It is suggested that "is in sequence alignment with SEQ ID NO:1 (Clytin) and" be deleted.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have

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been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the biomolecule, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed biomolecule."

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

These claims are directed to a genus of clytin variants and fragments thereof. However, the claims include no requirement that the recited fragments have any functional activity as a photoprotein nor that the recited fragments have the properties listed in parts a)-c) of claim 1. As such the claims could be

reasonable interpreted as encompassing any photoprotein as there are no clear structural or functional limitations recited for the fragments. The specification teaches the structure of only a few representative species of such clytin variants. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having photoprotein activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants appear to believe that the amendment of the claims to delete "functional derivatives" would overcome the instant rejection. However, this is not the case as the amendments to the claims also altered the scope of "fragments" claimed. As such the rejection is maintained.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for clytin variants having 90% identity to SEQ ID NO:1 and comprising a G₁₄₂→C substitution at the position corresponding to G₁₄₂ of SEQ ID NO:1, does not reasonably provide enablement for any photoprotein comprising any fragment of a clytin variant

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having 90% identity to SEQ ID NO:1 and comprising a G₁₄₂→C substitution at the position corresponding to G₁₄₂ of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1 and 5 are so broad as to encompass any photoprotein comprising any fragment of a clytin variant having 90% identity to SEQ ID NO:1 and comprising a G₁₄₂→C substitution at the position corresponding to G₁₄₂ of SEQ ID NO:1. It should be noted that the recited fragment could be as small as dipeptide as the claims include no requirement that the recited fragments have any functional activity as a photoprotein nor that the recited fragments have the properties listed in parts a)-c) of claim 1. As such the claims could be reasonably interpreted as encompassing virtually any photoprotein as there are no clear structural or functional limitations recited for the fragments and all photoproteins will comprise at least one dipeptide within the structure of SEQ ID NO:7. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of photoproteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and

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functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a few specific clytin variants (i.e., SEQ ID NOS:2-10).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any photoprotein comprising any fragment of a clytin variant having 90% identity to SEQ ID NO:1 and

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comprising a G₁₄₂→C substitution at the position corresponding to G₁₄₂ of SEQ ID NO:1 because the specification does not establish:

(A) regions of the protein structure which may be modified without effecting photoprotein activity; (B) the general tolerance of photoproteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any photoprotein comprising any fragment of a clytin variant having 90% identity to SEQ ID NO:1 and comprising a G₁₄₂→C substitution at the position corresponding to G₁₄₂ of SEQ ID NO:1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of clytin variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

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unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants appear to believe that the amendment of the claims to delete "functional derivatives" would overcome the instant rejection. However, this is not the case as the amendments to the claims also altered the scope of "fragments" claimed. As such the rejection is maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Prasher (US Patent 5,360,728).

Prasher teach several aequorin variants (SEQ ID NOS 3-5 of Prasher) having enhanced bioluminescence compared to wild type aequorin. These photoproteins comprise the amino acid sequence DVDEMTRQHLGFWYT (residues 169-183 of SEQ ID NOS 3-5 of Prasher) which is a fragment (i.e., residues 170-184) of SEQ ID NO:7 (i.e. a protein which meets all limitations of parts a)-c) of claim 1).

Applicants argue that that Prasher does not disclose each element of claim 1 as the aequorin variants disclosed in Prasher do not show at least 90% identity to SEQ ID NO: 1 (clytin) as recited in claim 1. However, claim 1 as amended does not require that the claimed photoprotein have 90% identity to SEQ ID NO:1 but merely that it comprise a fragment of a protein having 90% identity to SEQ ID NO:1 (and meeting the limitations of parts a) and c) also). The proteins of Prasher have photoprotein activity and comprise a fragment of SEQ ID NO:7 herein as discussed above. SEQ ID NO:7 herein is a photoprotein meeting all limitations of parts a)-c) of claim 1. Therefore as Prasher disclose photoproteins comprising a fragment of a protein meeting the limitations of parts a)-c) of claim 1, these proteins meet all requirements of claim 1.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Tsuzuki et al.

Tsuzuki et al. teach several aequorin variants having enhanced bioluminescence compared to wild type aequorin. These photoproteins comprise the amino acid sequence DVDEMTRQHLGFWYT which is a fragment (i.e., residues 170-184) of SEQ ID NO:7 (i.e. a protein which meets all limitations of parts a)-c) of claim 1).

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Applicants argue that that Tsuzuki et al. does not disclose each element of claim 1 as the aequorin variants disclosed in Tsuzuki et al. do not show at least 90% identity to SEQ ID NO: 1 (clytin) as recited in claim 1. However, claim 1 as amended does not require that the claimed photoprotein have 90% identity to SEQ ID NO:1 but merely that it comprise a fragment of a protein having 90% identity to SEQ ID NO:1 (and meeting the limitations of parts a) and c) also). The proteins of Tsuzuki et al. have photoprotein activity and comprise a fragment of SEQ ID NO:7 herein as discussed above. SEQ ID NO:7 herein is a photoprotein meeting all limitations of parts a)-c) of claim 1. Therefore as Tsuzuki et al. disclose photoproteins comprising a fragment of a protein meeting the limitations of parts a)-c) of claim 1, these proteins meet all requirements of claim 1.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of Prasher (US Patent 5,360,728) or Tsuzuki et al.

Each of Prasher and Tsuzuki et al. teach aequorin variants having enhanced bioluminescence compared to wild type aequorin. They do not specifically teach the addition of a mitochondrial targeting sequence to the amino terminus of said variants. However, the use of photoproteins as reporter proteins for calcium concentrations in various subcellular localities is well known in the art as are targeting sequences for most subcellular organelles (i.e., nuclear localization signals, mitochondrial localization signals, ER targeting signals, peroxisome targeting signals, etc.). Therefore it would have been obvious to one of ordinary skill in the art to fuse the aequorin variants of Prasher or Tsuzuki et al. to a subcellular targeting sequence in order to use the variants as a reporter protein for calcium concentrations within these organelles.

Applicant has not presented any arguments specifically traversing this rejection but instead relies upon the traversal discussed above. Therefore, this rejection is maintained for the reasons presented above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached at (571) 272-0956. The fax phone number for this Group is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
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